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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 08/465,596	Applicant(s) Selden
	Examiner Christopher S. F. Low	Group Art Unit 1633

☒ Responsive to communication(s) filed on *8 Dec 1998 and the prior supplementatl response of 25 Junew 1998* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *72-80, 82-95, and 97-103* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *72-80, 82-95, and 97-103* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Insofar as the present response refers to a supplemental response and declaration filed 25 June 1998 (USPTO Group 1600 date of receipt) and which did not cross in the mails that amendment and declaration is considered in this Office Action along with the amendment filed 8 December 1998 in connection to the invention as presently claimed. The amendment filed 8 December 1998 is noted as (A) canceling claims 81 and 86; (B) amending claims 72, 78, 79, 84-87, 93, 94, 99, and 100; and, adding claims 102 and 103. In view of the amendments to the claims, the following are or remain applicable to pending claims 72-80, 82-95, and 97-103.

The supplemental response filed 25 June 1998 which presents no amendments to any claim has been considered below in the appropriate sections of this Office Action. The mailing address has been corrected to reflect applicant's current representative as requested (response of 8 December 1998 at page 6).

Objection and Rejection for New Matter

The amendment filed 8 December 1998 is objected to under 35 U.S.C. 132 because it introduces new matter into the specification. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows.

The amendment filed 8 December 1998 is objected to under 35 U.S.C. 132 because it introduces new matter into the specification. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows in item (a) of claim 72 which is:

> " and without using a viral vector to introduce the DNA into cells, wherein the DNA sequence comprises no DNA of retroviral origin"; and,

the item (a) recitation in claim 87 of:

> "and without using a retroviral vector to introduce the DNA into cells, wherein the DNA sequence comprises no DNA of retroviral origin".

The above recitation in the claims has no apparent explicit or implied antecedent basis nor any apparent definition in the in the specification as originally filed. Similar language in newly presented claims 102 and 103 are objected to as containing new matter. The above recitations in the claims

have no apparent explicit or implied antecedent basis nor any apparent definition in the specification as originally filed.

Where the present amendment (pages 11-15) refers to Paper 16 at pages 2 and 3, cites *Vas-Cath, Inc. v. Marhurkar* in reference to the 11 March 1998 amendment, regarding the above claim terminology, as well as the Goodman declaration, the comments are unpersuasive as none of page 4 (lines 16-21), 5 (line 32)to page 6 (line 4), and page 6 (lines 21-25, 28-31 and 25-31) of the application that the prior response referred to support the present claim 72 language of

> " and without using a viral vector to introduce the DNA into cells, wherein the DNA sequence comprises no DNA of retroviral origin"; nor,

the item (a) recitation in claim 87 of:

> "and without using a retroviral vector to introduce the DNA into cells, wherein the DNA sequence comprises no DNA of retroviral origin".

None of these pages contain any recitation that describes the claim language nor suggests the present claim language. As to the item (a) recitation indicated above in claim 87, page 13 of the application, like pages 4-6 of the application do not contain any recitation that describes the claim language nor suggests the present claim language. Thus, it is not apparent where in the written description as originally filed that the above indicated terminology is found. These pages of the application do not contain the phraseology discussed above nor do these pages of the application indicate that the genetic material used contains no retroviral DNA nor are the cited passages of the application interpretable as meaning what is recited in the claims. As to the foregoing, claims 102 and 103 are also included and are objected to as introducing new matter.

Pages 12-13 of the 8 December 1998 response cited items 20-25 of the Goodman declaration as standing for indication that the present application did not use retroviral vectors as discussion of retroviral vectors, retroviral promoters, *ex vivo* gene therapy, and reference to pages 18-19 and to the examples in the specification. The comments are not persuasive because specification pages 18-19 to which the response at page 12 refers and to which item 21 of the Goodman declaration refers do not describe, suggest nor indicate that no retrovirus DNA is to be used nor that no viral vectors are to be used. Item 22 (cited from the Goodman declaration) bridging pages 12-13 of the response is noted as to the commentary regarding gene therapy and *ex vivo* gene therapy in reference to page 6 at lines

27-31 of the present application specification (exhibit 4 of the Goodman declaration). The fact that this passage of the specification refers to disadvantages of certain vectors is noted but the specification passage cited does not state nor suggest that nor contain terminology indicative of "do not use viral nor retroviral vectors". There is no explanation in items 20-25 of the Goodman declaration demonstrating how the present claim terminology is obtained from these sections of the present specification.

Regarding item 23 of the Goodman declaration, the reference to specification pages 12 and 13 are argued as support for not using retroviral or viral vectors. The comments are unpersuasive since the cited pages do not state nor suggest nor contain terminology indicative of "do not use viral nor retroviral vectors". There is no explanation in items 22 of the Goodman declaration demonstrating how the present claim terminology is obtained from these sections of the present specification. Pages 12-13 refer to the drawings in the application. No drawings indicate the absence of nor contain indicia of not using viral nor retroviral vectors or DNA and many if not the majority of the references cited in the application for teaching how to transfect/transform cells use viral and/or retroviral vectors. The instant application contains only one disclosed vector, example 1. That vector is pXGH5. The vector as indicated in the Selden *et al.* (1986) Molec. Cell. Biol. 6(9): 3173-3179 as containing genetic material from pUC12 which is referenced in the publication by reference 20 which is a reference by Vieira *et al.* (1981) Gene 19: 259-268. The Vieira *et al.* reference disclosed that pUC12 contains genetic material from M13, a virus. Thus, the application does not disclose a vector that contains no viral and/or no retroviral genetic material and pages 12-14 and items 20-25 in the Goodman declaration are unpersuasive for the reasons indicated above.

It is further noted that pages 14-15 of the present response refer to *Vas-Cath Inc. v. Mahurkar* and the *Ralston-Purina Co. v. Far-Mar Co., Inc.* decisions in connection with the Goodman declaration. The comments are unpersuasive for the reasons indicated above since the specification and the declaration do not demonstrate what is asserted in the declaration. The additional comments regarding pXGH5 and pHINT5 are unpersuasive since pXGH5. The vector is indicated in the Selden *et al.* (1986) Molec. Cell. Biol. 6(9): 3173-3179 as containing genetic material from pUC12 which is referenced in the publication by reference 20 which is a reference by Vieira *et al.* (1981) Gene 19: 259-268. The Vieira *et al.* reference disclosed that pUC12 contains genetic material from M13, a

virus. The comments in the first two full paragraphs of response page 15 do not provide persuasive rebuttal. It is apparent that there is no disclosure in the application as filed for the present claim terminology and the present claim terminology introduces new matter into the application.

Rejections under 35 U.S.C. 112 first paragraph

New Matter

Claims 72-80, 82-95, and 97-103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention as to the presently recited new matter as discussed in the above objection to the claims.

The foregoing objects to the amendment and rejects the claims on the basis of new matter. Applicant is required to cancel the new matter in the response to this Office Action.

Enablement

Claims 72-80, 82-95, and 97-103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention; and claims 72-80, 82-95, and 97-103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which is most nearly connected, to make and/or use the invention, i.e., the claims are not enabled by the present application written description as presently claimed.

The instant application contains only one disclosed vector, example 1. That vector is pXGH5. The vector as indicated in the Selden *et al.* (1986) Molec. Cell. Biol. 6(9): 3173-3179 as containing genetic material from pUC12 which is referenced in the publication by reference 20 which is a reference by Vieira *et al.* (1981) Gene 19: 259-268. The Vieira *et al.* reference disclosed that pUC12 contains genetic material from M13, a virus. Thus, the application does not disclose a vector that

contains no viral and/or no retroviral genetic material. The neither the present application nor the present response refer to any vectors that contain no viral genetic material nor any vectors that contain no retroviral material. Specification pages 4-6 and 13 that the response filed 11 March 1998 refers to have been considered in this regard and for the reasons indicated in the above objection for new matter and rejection for new matter under 35 U.S.C. 112 first paragraph, the specification does not teach or suggest the absence of viral and/or retroviral material from the vectors. There is also no explicit teaching of a vector that contains no viral DNA or no viral RNA even where the instant application disclosure indicates that there are obstacles. Pages 17+ and 33+ of the application contains no disclosure that the vectors contain no viral and/or nor retroviral DNA (retroviruses do not contain DNA). Page 35+ refers to using viral DNA as a selected gene sequence which is directly contrary to the instant claim recitation. The present claims also indicate selecting for free from deleterious integration events but does not define nor disclose how such events are to have detected and cells containing same removed from the selected cell population. In this regard, page 4 of the application contains no written description of the instant claims and no enabling disclosure that guides one skilled in the art and pages 15+ of the application do not define same.

The comments at pages 15-21 of the response filed 8 December 1998 have been considered but are unpersuasive. The commentary in the paragraph bridging pages 15-16 is noted as referring to the prior Office Action. From that prior Office Action it was indicated (and is restated herein as remaining applicable to the present application claims and argument presented in the 8 December 1998 response that where pages 14-21 and 22-40 of the response filed 11 March 1998 discussed the prior Office Action rejection under 35 U.S.C. 112 first paragraph, the comments remain unpersuasive in view of the above stated ground of rejection even where page 14+ cites and refers to the *Vas-Cath Inc. v. Mahurkar* decision as to one skilled in the art and to what is claimed. For the reasons indicated in the preceding paragraph, the facts in this application differ from the cited decision. The discussion of the Robertson *et al.* reference remains unpersuasive and does not address the stated rejection. As to the discussion of proviruses (pages 16-17+, response filed 11 March 1998) the comments are unpersuasive as to teaching the recited claim terminology. As to the citation of the *Ralston-Purina Co. v. Far-Mar Co., Inc.* and the *Ex parte Yamaguchi* decisions the comments are also unpersuasive since the even where applicant would argue that the claim need not be described literally, there is no

indication that the disclosure meant to exclude virus and/or retrovirus since as discussed in the application written description, all that is indicated is that there are problems with viral and/or retroviral vectors but not that the application intended to exclude same. The lone exemplified vector contains viral genetic material. Thus, it is not apparent that the claims are supported by a written description nor does the written description enable the present claims.

The page 19+ discussion (response filed 11 March 1998) of Transkaryotic Therapies, Inc. is noted, however, the presence or the absence of the company is not an issue for enablement nor for written description of the instant claims and is unpersuasive. In this paragraph, the citation of the Selden (1987) N. Eng. J. Med. and Science references have been considered, however, the Science paper and the N. Eng. J. Med. were both published after applicant's filing date of 1 May 1987 in the 07/044,719 application nor do either reference refer to the instant '719 application and both references disclose the presence of viral genetic material in the constructs used. Thus, neither reference supports the present claims nor the application disclosure as to the resent language in the claims.

As to pages 22-40 in the 11 March 1998 response, the comments are also unpersuasive as to the page 23+ discussion regarding all genes as transferred via a nonviral and/or nonretroviral construct since those constructs are not disclosed nor *per se* suggested even where the claims (page 24, response filed 11 March 1998) are asserted to refer to gene transfer as opposed to gene therapy. The present application does not disclose where nor indicate that the transfer is for anything but for gene therapy and that the vector used (and which is the only disclosed vector) contains viral genetic material. Thus, the claims are not enabled nor described in the application as originally filed. The page 25 (response filed 11 March 1998) discussion of gene transfer is noted, but unpersuasive as to explicit description in the application as filed nor suggestion in the application as filed nor by exemplification in the application as filed. As indicated above, the lone vector disclosed in the application contains viral genetic material and therefore, does not demonstrate the claims which are asserted to require the absence of a viral vector, i.e., a vector that contains no viral or retroviral genetic material. In this regard, the response (pages 26-27, response filed 11 March 1998) refer to *In re Marzocchi*, *In re Jolles*, and *Application of Hartop*, *In re Brana*, *Raytheon Co. v. Roper Corp.* as to compliance with 35 U.S.C. 112 and support for broader claims. The comments are unpersuasive since

the present claims have nor explicit, implicit nor suggested disclosure in the present application as filed. As to the cited decisions, the present response does not demonstrate where in the application as filed that such disclosure is present in the application and confuses the utility guidelines under 35 U.S.C. 101 with the requirements under 35 U.S.C. 112 first paragraph as to written description and enablement based upon that written description.

Insofar as the response of 11 March 1998 at pages 28+ cite and discuss example 10 and references by Like *et al.*, Stearns *et al.*, and Schwab *et al.*, it is not clear nor apparent where in the application nor in example 10 that the references are relied upon. The references do not appear to have been cited in the application in the example nor does the response point to any part of the application that cites these references. What is not disclosed (or cited in the application) cannot be used for enablement nor for written description nor for best mode. Pages 28+ of the 11 March 1998 present response refer to the Geisen declaration. The declaration does not discuss the present claims and is ineffective.

The page 30+ (response filed 11 March 1998) discussion of immunosuppressive therapy is noted as asserted to be an optional embodiment, however, specification pages 20, 33-34, 38, 46-47, and specification examples 6-7 do not discuss, suggest, nor exemplify the presently claimed invention defined in claims 71 and 87. As to the page 31 (response filed 11 March 1998) discussion of the Cao *et al.* reference, it is published long after applicant's filing date, does not disclose the state of the art at the time the original application was filed, and does not disclose the presently claimed invention, but does disclose having used a BMGNeo vector which contained 69% bovine papilloma virus genome and thus, is a reference disclosing having used vectors containing viral genetic material and unpersuasive.

Pages 32+ (response filed 11 March 1998) assert that the specification is enabling for animals and genes not used in the examples. The comment is noted but unpersuasive as to the present claims, e.g., 72 and 87 and the claims dependent thereto and cites *Ex parte Balzarini*, however, the present claims are not supported in the application as filed by disclosure nor tests demonstrative of genetic constructs that contain no viral and/or nor any retroviral genetic material. In the present

application, there are no disclosed tests of the instant vectors that are recited in the claims as having no viral and/or no retroviral genetic material. Thus, the facts differ from that of *Ex parte Balzarini*, however, the rejection present rejection is not for scope but for nonenablement which is issue under 35 U.S.C. 112 first paragraph considered in the "REJECTION 1" indicated in the decision and is affirmed.

Reviewed anew, the commentary at pages 15-21 are also unpersuasive for the following reasons. The paragraph bridging pages 15-16 is noted as to the citation of *In re Marzocchi* regarding reasoned doubt. Such reasoned doubt is clearly presented in the stated rejection and in the above indicated paragraphs. The commentary at page 17 regarding the Geissen declaration is noted but is also not persuasive since the declaration has been considered in a prior Office Action and what is not disclosed (or cited in the application) cannot be used for enablement nor for written description nor for best mode. The comments at page 16 are unpersuasive since they do not demonstrate that the vectors pXGH5 and pHINT5 do not contain (A) viral DNA nor contain (B) DNA of retroviral origin. There is no establishment of 35 U.S.C. 112 first paragraph complacence. In the prior Office Action, it was indicated that pages 28+ of the 11 March 1998 present response referred to the Geisen declaration. The declaration does not discuss the present claims and is ineffective and is consideration of the declaration. It is also noted that applicant's response again demonstrates misapplication of the statute and criteria applied in the stated rejection since the rejection is made under 35 U.S.C. 112 first paragraph. 35 U.S.C. 112 first paragraph is not a utility rejection.

The comments at page 18 discuss commentary similar to if not identical to the prior response of 11 March 1998 and as discussed above, the Selden *et al.* reference in the N. Eng. J. Med. which for the above discussed reasons is unpersuasive and does not show the presently claimed invention. As to each of the Kawakami *et al.*, Simpson *et al.*, and Lauffenberger *et al.* references, each is published after the present application was filed in 1987 and thus, cannot be used to show enablement. In this regard applicant relies upon Gould v. Quigg, *In re Marzocchi*, and *In re Brana* for support. In this instance, discussion nor the references demonstrate that as of the time of applicant's filling that applicant disclosed using a vector that was not viral nor retroviral nor used a vector that that had no

DNA of viral origin nor any DNA of retroviral origin. These decisions rest on facts different from the present fact and fact pattern.

Insofar as the last full paragraph of page 18 and the first full paragraph of page 19 refer to the Cao *et al.* reference, it has been discussed in the previous Office Action and in the preceding paragraphs. The additional allegation regarding dismissing the reference is unpersuasive and devoid of fact. The reference was considered and is demonstrative that the Cao *et al.* reference was published long after applicant's filing date, does not disclose the state of the art at the time the original application was filed, and does not disclose the presently claimed invention, but does disclose having used a BMGNeo vector which contained 69% bovine papilloma virus genome. Thus, this reference disclosed having used vectors containing viral genetic material and unpersuasive in regard to applicant's allegation of dismissing the reference. Insofar as applicant now asserts the reference demonstrates use of immunosuppression, the present claims do not call for same. Applicant's response alleges the reference is irrelevant.

Pages 19-21 discuss various references cited in prior Office Actions. As previously discussed, the (pages 33+, response filed 11 March 1998) Orkin *et al.* and the Crystal references is noted, but unpersuasive as to the present claims for the reasons indicated above. At page 36 (response filed 11 March 1998), applicant's response refers to the *In re Glass* and the *U. S. Steel v. Philips Petroleum Co.* decisions as to references discussing the state of the art after applicant's filing is noted, however, neither the response nor the decisions indicate how the state of the art is more advanced or enabling at the time of filing than some several years later. When the art cited considers and presents doubts as to success at a time after applicant's filing, it cannot be said that at a time prior, that the application was enabling even where applicant's response alleges at page 19 that the references are irrelevant in the 8 December 1998 response. These references are not irrelevant.

At pages 37+ (response filed 11 March 1998) applicant's response refers to others as recognizing novel/pioneering work by citing the Kawakami *et al.* (1992) Diabetes 41: 956-961, however, the reference disclosed having used a vector that contained 69% papilloma virus sequences. Thus, the reference does not demonstrate applicant's claim and indicates that 1/10th of the material

was used compared to references 2 and 4 cited in the Kawakami *et al.* reference wherein the Kawakami *et al.* reference did not even use a vector that contained no viral genetic material nor is such predicted by the present application disclosure. In the present 8 December 1998 response it is alleged that the results of the reference are misconstrued. The comment in the response is not factually based for the reasons indicated above.

As previously pointed out the Simpson *et al.* (1995) Gene Therapy 2: 223-231 reference is also noted as to the reference to "footnote 2" but page 223 contains no footnote. As to the comment of referring to reference 2 that is cited at page 230 of the Simpson *et al.* reference, the Selden *et al.* reference in the N. Eng. J. Med. does not disclose a vector that was used that had no viral genetic material but does disclose pHINT5 which contains genetic material from pUC18 (figure 4 of the Selden *et al.* reference) which absent factual evidence to the contrary, contains genetic material from a virus and pHINT5 is not apparent nor disclosed in the present application and the reference disclosed that the mice died of transkaryotic implantation induced hypoglycemia, i.e., the reference demonstrates a lack of control of gene expression. At page 38 (response filed 11 March 1998), it is also noted that the response refers to a reference by Lauffenberger *et al.* (1996) and especially page 71 column 1 as to nonviral gene therapy. It is noted that the Lauffenberger *et al.* reference refers to the Selden *et al.* reference in the N. Eng. J. Med. which for the above discussed reasons is unpersuasive and does not show the presently claimed invention. As to each of the Kawakami *et al.*, Simpson *et al.*, and Lauffenberger *et al.* references, each is published after the present application was filed in 1987 and thus, cannot be used to show enablement. In view of the foregoing the comments at pages 15-21 of the response filed 8 December 1998 are unpersuasive.

Obviousness-type double patenting rejections

The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321 (b) and (c) may be used to overcome actual or provisional rejection(s) based on non-statutory double patenting ground(s) of rejection set forth below provided the conflicting application(s) or patent(s) is/are shown to be commonly owned with this application. See 37 C.F.R. 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 C.F.R. 3.73(b).

Claims 72-80, 82-95, and 97-103 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over pending claims 91-126 in copending application Serial No. 08/461,292. Each of the applications contain claims in which a processes of implanting transformed cells is recited where the transformed cells express DNA that was inserted into the cells prior to implantation.

Claims 72-80, 82-95, and 97-103 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 44 in copending application Serial No. 08/460,902. Each of the three applications contain claims to processes of implanting transformed cells where the transformed cells express DNA that was inserted into the cells prior to implantation. Here, altering the concentration of a gene product is the same as expressing the gene to produce a product in the '292 application and of putting those cells which express the gene into a host as in the '902 application.

Claims 72-80, 82-95, and 97-103 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims in copending application Serial No. 08/465,582. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are an obvious variation of the claims in the pending '582 application since in each application but in different words, the sets of claims recite implanting a transformed cell to produce an effect in a human, i.e., *in vivo* therapy which implants a cell or cells but which cells have, *ex vivo*, been transformed prior to implantation. The present claims

also do not define over the interference count. Regardless of the vector, viral or nonviral and which in this instance, the vectors are obvious variations of effecting gene transfer into the implanted cells, the process of therapy and the intended end result is the same.

Claims 72-80, 82-95, and 97-103 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the allowed claims of copending application serial no. 08/451,894. Although the claims are not identical, each set of claims recite providing a genetically altered cell to a mammal (copending application) or to an animal (present application) each of which deliver a gene construct to cells which are then reintroduced into the animal. Therefore, the two applications claim the same inventive concept.

Claims 72-80, 82-95, and 97-103 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 68-77 and 105-107 of copending application serial no. 08/446,909. Although the claims are not identical, each set of claims recite a process of providing genetically altered cells (in the copending application, the DNA encoding erythropoietin is a desired gene such as recited in the present application claims) to a mammal (copending application) or to an animal (present application) each of which isolate the cells, introduce the genetic material into cells, and then reintroduce selected genetically altered cells into the animal.

Claims 72-80, 82-95, and 97-103 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 96-104 of copending application serial no. 08/446,912. Although the claims are not identical, each set of claims recite a process providing a genetically altered cell (in the copending application, the DNA encodes a glucagon-like peptide 1 is a desired gene such as recited in the present application claims) to a mammal (copending application) or to an animal (present application) each of which transfer a gene to the cells and then reintroduce the cells into the animal. Therefore, the two applications claim the same inventive concept.

Claims 72-80, 82-95, and 97-103 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 125-134 of copending application serial no. 08/443,936. Although the claims are not identical, each set of claims recite a process which provides genetically altered cells (in the copending application, the DNA encodes a therapeutic peptide is a desired gene such as recited in the present application claims) to a mammal (copending application) or to an animal (present application) each of which also indicate the transfer of genetic material. In both applications, the genetic material is for expression by the implanted or administered cells. Therefore, the two applications claim the same inventive concept.

As to each of the above stated rejections for obviousness type double patenting, the comments at pages 21-22 of applicant's response filed 8 December 1998 has been considered but the comment of will "deal with on the merits when the subject application is found to contain allowable subject matter". The comments are unpersuasive because these would be standing grounds of rejection and no claims are allowable with a standing ground of rejection.

35 U.S.C. 112 second paragraph rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 72-80, 82-85, and 87-103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In clams 72 and 87 it is not clear whether the "and without using a viral vector to introduce the DNA into the cells" now means no viral DNA in the DNA as now it only has to be of nonretroviral origin or whether it is to mean that an intact virus is not the transforming genetic material. Claims 78, 84, 85, 93, and 99 are unclear as to what steps are included or excluded in "comprises" recited in the claim as opposed to "has a step" since, e.g., claim 78 is now written as an open ended Markush claim which is also indefinite. This is also necessitated by applicant's amendment to the claims. Claims 80 and 81 do not further limit nor is it clear that claim 73 nor claim 72, and, claims 95 and 96 do not further limit claims 88 nor 87 because both claim 72 and 87 are asserted to require the absence of viral genetic

material which therefore means that there is no viral promoter nor any retroviral promoter that can be included in claim 72 nor claim 87 as presently recited in the independent claims. Since this limitation is already in the independent claims, it is not apparent how the recitation in the above claims further limits the independent claims. Claim 101 lacks antecedent basis in claim 88 and 87 for "in the genome of the recipient subject". In claims 85 and 100 it is not clear what is the deleterious integration event to which the claim refers nor how a preexisting deleterious event is eliminated nor whether or not the transforming event eliminates a deleterious integration event. In claim 84 and 99, it is not clear what are the "desired expression properties" and whether or not the regulation affects the genetic material that is added to the cell or whether the regulation affects some other preexisting genetic material in the cells prior to transfection.

Regarding the stated rejection under 35 U.S.C. 112 second paragraph, the comments (pages 22-25) in the response filed 8 December 1998 are unpersuasive. The comments at page 22 (first paragraph under the discussion of the indefiniteness rejection) to the end of the second full paragraph of page 22 have been considered as to the stated ground of rejection but are unpersuasive in the manner in which the claims have been amended as stated in the ground of rejection above. Insofar as the first two full paragraphs of page 23 refers to not excluding "viral DNA", the claim is also argued in prior responses as not having or using a viral vector – indicative that there is no viral DNA and therefore the claim cannot have a viral promoter. It is clear that applicant's claim is indefinite since it is applicant's argument that presents alternative interpretations of the claim(s). The cancellation of claims 81 and 86 are noted and the rejection does not now recite same. In the fourth full paragraph of page 23, the comment regarding "recipient subject" is noted but the claim lacks antecedent basis for "in the genome of the recipient subject".

In the paragraph spanning pages 23-24 the response refers to specification page 4 in regard to the "deleterious integration event" but that passage from the specification does not define what is or are nor disclose how to identify such events. The passage from the specification does not present any clarity for the claim nor define the terminology. Insofar as the first full paragraph of page 24 refers to the Robertson article in discussion of DNA of retroviral origin, retroviruses are RNA and do not have DNA and even where the Robertson reference is discussed in the Goodman declaration in reference to

the assertion that one skilled in the art would recognize a deleterious integration event in regard to retroviruses, applicant asserts by claim terminology that there DNA used has "no DNA of retroviral origin" and thus, the declaration item and reference are ineffective, since the comments address a nonexistent deleterious integration event (no retrovirus, no deleterious integration event due to retrovirus). This commentary in the applicant's response does not make the claim(s) definite.

In the paragraph spanning pages 24-25, the present response refers to claims 84 and 99 and desired regulation properties as having been amended to indicate desired expression properties. Reference is made to Figure 1 and specification pages 12-13 as support for "desired expression properties", however, the cited pages and passage do not define what are or are not desired as expression properties at all. This passage does not make the claims definite nor apprise anyone of skill or ordinary skill in the art as to what is/are or is/are not desired as desired expression properties.

Claim 80 is rejected under 35 U.S.C. 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 80 does not further limit claim 73 nor claim 72, and, claim 95 does not further limit claims 88 nor 87 because both claim 72 and 87 require the absence of viral genetic material which therefore means that there is no viral promoter nor any retroviral promoter that can be included in claim 72 nor claim 87.

The commentary at page 25 regarding the 35 U.S.C. 112 fourth paragraph rejection is noted in the 8 December 1998 response but is not persuasive for the reasons indicated in the stated rejection. The comment referring to the rejection under 35 U.S.C. 112 second paragraph as overcoming the rejection and thus, the fourth paragraph rejection as well is unpersuasive for the reasons stated in the rejection under 35 U.S.C. 112 second paragraph. The rejection is easily overcome by (1) canceling the claims or (2) properly amending the claims. Not amending the claims and reference to the rejection under 35 U.S.C. 112 second paragraph do not remove the rejection.

35 U.S.C. 102 and 103 rejections over art

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless

(f) he did not himself invent the subject matter sought to be patented; or

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Insofar as applicant has amended all of the claims, the following are applicable to pending claims 72-103 as directed solely to compositions.

Claims 72-80, 82-95, and 97-103 stand provisionally rejected under 35 U.S.C. 102(f) or (g) or in the alternative, under 35 U.S.C. 103(a) as being unpatentable over the count and disclosure of the application of the winning party in the interference, which count recites a method of therapy in which cells are transformed and then implanted into the host human or other mammal after selection *ex vivo* which are the presently recited cells in the process claims.

The response at page 25 is noted as to applicant's comment regarding traverse of the rejection, however, it is not persuasive as the commentary of "will deal with it on the merits when the subject application is found to contain allowable subject matter" does not address the rejection and these are and would remain as standing grounds of rejection. No claims are allowable with a standing ground of rejection remaining.

The prior Office Action indicated the Salser *et al.* reference, applicant's prior response (pages 47-48) asserted methotrexate is disclosed as used in the Salser *et al.* reference, however, the reference indicated (column 6) that upon cessation of the treatment, the cells continue to proliferate and are maintained as a high level for extended periods of time and at column 1-2 indicates that such stressing of the host is optional. The discussion at page 48 of the prior response regarding promoters and the Salser *et al.* reference is noted, but for the reasons indicated in the stated rejection the comment is unpersuasive. As to the Anderson reference, pages 40-49 of the prior response do not appear to contain any discussion thereof but the reference nevertheless teaches vectors that do not contain viral or retroviral genetic materials as discussed in the above stated rejection.

Claims 72-75, 78-80, 82-90, 93-95, and 97-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined references of Salser *et al.* (US 4,497,796) and Anderson (1984) Science 226: 401-408.

Salser *et al.* disclosed a process (column 1-2 *et seq.*) in which cells were genetically altered to contain modified genes (a wide variety of genes, columns 2-4). The cells were reintroduced (column 2+) in a variety of ways (column 6) into the mammal and directed, via the gene construct(s), expression of the exogenous DNA (see at least column 3+). See at least the abstract and the claims. The reference also teaches (column 5) that among the vectors used, certain combinations such as cell fusion and, e.g., using a plasmid such as indicated in the Salser *et al.* and the Anderson references (Anderson at 406+) are expected to not contain viral or retroviral genetic material. In the disclosed process, the reference (column 2) teaches maintaining the cells *in vitro* (i.e., cloning and expanding the cells) so as to be returned to the host in a viable state (i.e., absence of deleterious integration events

such as inviable cells) and so as to provide the added genetic function in a form which is useful to the host which is a teaching to culture the cells *in vitro* and to use the cells that contain and express the added genetic function in a form which is useful to the host, i.e., in alternative language to the present claims, a teaching of selecting cells possessing the desired characteristics. Here, where Salser *et al.* do not explicitly indicate a promoter type (column 4-5), Salser *et al.* nevertheless indicated obtaining expression and of constitutive and/or semiconstitutive production (column 4) and for expression a promoter is necessarily present. Here, where the Salser *et al.* reference does not explicitly indicate a promoter type, the Anderson reference disclosed (page 405-406) that various types of expression control DNA were known and had been used to regulate expression. Note that it would have also been obvious to anyone of ordinary skill in the art that autologous cells would have minimized adverse immunological effects of the implanted cells and the host animal. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 76, 77, 91, and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined references of Salser *et al.* (US 4,497,796) and Anderson (1984) Science 226: 401-408 as applied to claims 72-75, 78-80, 82-90, 93-95, and 97-103 above and further in view of Sugimoto *et al.* (US 4,621,053).

Salser *et al.* and Anderson are applied as indicated above and where the Salser *et al.* reference indicates proteins such as hormones (column 2) it would have been obvious to one of ordinary skill in the art that both insulin and hormones such as growth hormone as both genes are known and both genes are discussed in the Sugimoto reference which teaches implanting cells that have been genetically altered to produce hormones and disclosed among other genes, those for insulin and growth hormone (column 2). See also column 4+ and column 6 which disclosed that

> "As long as the "hybridoma" cell line is basically a lymphoblastoid line, preferably of leukemic origin, which contains the genes governing the production of the human peptide hormone in question, it may be used in the process of the present invention. For example, the human peptide hormone production governing genes may be introduced into the lymphoblastoid line, preferably of leukemic origin, by means of genetic engineering techniques, such as recombinant DNA techniques, using enzymes such as DNA ligase, nuclease, and DNA polymerase. Thus, the term "human X human hybridoma lymphoblastoid line capable of producing human

> peptide hormone" as used throughout the present specification and claims is intended to include not only lymphoblastoid lines produced by cell fusion between parent human cells inherently capable of producing the human peptide hormone and the human lymphoblastoid line, but also to human lymphoblastoid lines which have been altered in any manner, such as by genetic engineering, so as to be capable of producing human peptide hormone.

Thus, where the present claims indicate no viral and/or no retroviral DNA, the vectors used in the combined references do not contain virus nor any retrovirus and that from the combined disclosure of the Salser *et al.* Anderson and Sugimoto *et al.* references, it would have been obvious to have delivered a cell that had been screened for production of, e.g., insulin and/or growth hormone into a host animal. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

No claim is allowed.

In regard to each of the above rejections under 35 U.S.C. 103, the comments at pages 26-27 in applicant's response do not separately discuss each stated ground of rejection. At page 26 the 8 December 1998 response refers to the *In re Dow Chemical Co.* (as to expectation of success), the *W. L. Gore and Assoc. Inc. v. Garlock* (as to the reference as a whole and teaching away from the claimed invention), *Inc* and *In re Gurley* (as to a direction different from the path taken by applicant) decisions. In the paragraph bridging pages 26-27, the 8 December 1998 response refers to the 11 March 1998 response as discussing numerous references teaching away from the claimed invention as to the asserted no viral vector and without using a retroviral vector. The comments in that 11 March 1998 response were considered and remain unpersuasive and as pointed out in response that 11 March 1998 response, the comments (pages 40-49) in the response have been considered insofar as they pertain to the above two references (both of record) but the comments are unpersuasive. As to the Salser *et al.* reference, applicant's response (pages 47-48) asserts methotrexate is disclosed as used in the Salser *et al.* reference, however, the reference indicates (column 6) that upon cessation of the treatment, the cells continue to proliferate and are maintained as a high level for extended periods of time and at column 1-2 indicates that such stressing of the host is optional. The discussion at page 48 regarding promoters and the Salser *et al.* reference is noted, but for the reasons indicated in the stated rejection the comment is unpersuasive. As to the Anderson

reference, pages 40-49 do not appear to contain any discussion thereof but the reference nevertheless teaches vectors that do not contain viral or retroviral genetic materials as discussed in the above stated rejection.

Applicant's amendment necessitated new/modified grounds of rejection. Accordingly, THIS ACTION IS MADE FINAL. See M.P.E.P. 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. in the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. in no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Low whose telephone number is (703) 308-2923. Inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission to Group 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1) and must conform to the notice published in the Official Gazette, 1096 OG 30 (15 November 1989). The telephone number assigned to Art Unit 1633 in the CM1 PTO Fax Center is (703) 308-4312.

CSFL
23 April 1999

Christopher S. F. Low

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1600